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Amendments to the Specification:

Please replace the "cross-reference to related applications" section with the following replacement section:

This application is a continuation of U.S. Application No. 09/580,015 filed May 26, 2000, which is a continuation-in-part of U.S. Application No. 322,289, filed May 28, 1999, which is a continuation-in-part of U.S. Application No. 09/201,430, filed November 30, 1998, which is a an application claiming the benefit under 35 U.S.C. 119(e) of U.S. Application Nos. 60/080,970, filed April 7, 1998, and 60/067,740, filed December 2, 1997. Each of the above applications is incorporated herein by reference.

~~This application is a continuation-in-part of USSN 09/322,289, filed May 28, 1999, which is incorporated by reference in its entirety for all purposes. This application is also a continuation-in-part of PCT/US98/25386, filed November 30, 1998, and USSN 09/201,430, filed November 30, 1998, both of which claim priority from USSN 60/080,970, filed April 7, 1998, and USSN 60/067,740, filed December 2, 1997. Each of the above applications and Townsend and Townsend and Crew Attorney Docket 015270-004750PC, filed May 26, 2000, is incorporated by reference in its entirety for all purposes.~~

Please replace the paragraph beginning on page 7, line 12 of the specification with the following replacement paragraph.

Fig. 10: Lymphocyte Proliferation Assay on spleen cells from AN1792-treated (Fig. 10A)~~(upper panel)~~ or PBS-treated (Fig. 10B) ~~(lower panel)~~.

Please replace the paragraph beginning on page 7, line 32 with the following replacement paragraph:

Fig. 19: Epitope Map: Restricted N–terminal Response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10–mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. ~~The results for peptide VGSNKGAII (SEQ ID NO:32) are shown twice.~~ Animal number F10920M shows a representative N–terminal restricted response to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide which was used as immunizing antigen.

Please replace the paragraph beginning at page 8, line 5 with the following replacement paragraph:

Fig. 20: Epitope Map: Non–restricted N–terminal response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10-mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. ~~The results for peptide VGSNKGAII (SEQ ID NO:32) are shown twice.~~ Animal number F10975F shows a representative non–restricted N–terminal response. Reactivity is seen against the two peptides N–terminal and one peptide C-terminal to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide.

Please replace the paragraph beginning at page 16, line 16, with the following replacement paragraph:

In a further variation, an immunogenic peptide, such as a fragment of Aβ, can be presented by a virus or a bacteria as part of an immunogenic composition. A nucleic acid encoding the immunogenic peptide is incorporated into a genome or episome of the virus or bacteria. Optionally, the nucleic acid is incorporated in such a manner that the immunogenic peptide is expressed as a secreted protein or as a fusion protein with an outer surface protein of a virus or a transmembrane protein of a bacteria so that the peptide is displayed. Viruses or bacteria used in such methods should be nonpathogenic or attenuated. Suitable viruses include

adenovirus, HSV, Venezuelan equine encephalitis virus and other alpha viruses, vesicular stomatitis virus, and other rhabdo viruses, vaccinia and fowl pox. Suitable bacteria include ~~Salmonella~~*Salmonella* and ~~Shigella~~*Shigella*. Fusion of an immunogenic peptide to HBsAg of HBV is particularly suitable. Therapeutic agents also include peptides and other compounds that do not necessarily have a significant amino acid sequence similarity with Aβ but nevertheless serve as mimetics of Aβ and induce a similar immune response. For example, any peptides and proteins forming β-pleated sheets can be screened for suitability. Anti-idiotypic antibodies against monoclonal antibodies to Aβ or other amyloidogenic peptides can also be used. Such anti-Id antibodies mimic the antigen and generate an immune response to it (*see Essential Immunology* (Roit ed., Blackwell Scientific Publications, Palo Alto, 6th ed.), p. 181). Agents other than Aβ peptides should induce an immunogenic response against one or more of the preferred segments of Aβ listed above (e.g., 1-10, 1-7, 1-3, and 3-7). Preferably, such agents induce an immunogenic response that is specifically directed to one of these segments without being directed to other segments of Aβ.

Please replace the paragraph beginning on page 46, line 21 with the following replacement paragraph:

The methods work by administering a reagent, such as antibody, that binds to Aβ in the patient~~to the patient~~, and then detecting the agent after it has bound. Preferred antibodies bind to Aβ deposits in a patient without binding to full length APP polypeptide. Antibodies binding to an epitope of Aβ within amino acids 1-10 are particularly preferred. In some methods, the antibody binds to an epitope within amino acids 7-10 of Aβ. Such antibodies typically bind without inducing a substantial clearing response. In other methods, the antibody binds to an epitope within amino acids 1-7 of Aβ. Such antibodies typically bind and induce a clearing response to Aβ. However, the clearing response can be avoided by using antibody fragments lacking a full length constant region, such as Fabs. In some methods, the same antibody can serve as both a treatment and diagnostic reagent. In general, antibodies binding to epitopes C-terminal of residue 10 ~~of Aβdo not~~of Aβ do not show as strong signal as antibodies

binding to epitopes within residues 1-10, presumably because the C-terminal epitopes are inaccessible in amyloid deposits. Accordingly, such antibodies are less preferred.

Please replace the paragraph beginning at page 59, line 25, with the following replacement paragraph:

Spleens were removed from nine AN1792-immunized and 12 PBS-immunized 18-month old PDAPP mice 7 days after the ninth immunization. Splenocytes were isolated and cultured for 72 h in the presence of Aβ40, Aβ42, or Aβ40-1 (reverse order protein). The mitogen Con A served as a positive control. Optimum responses were obtained with >1.7 μM protein. Cells from all nine AN1792-treated animals proliferated in response to either Aβ1-40 or Aβ1-42 protein, with equal levels of incorporation for both proteins (Fig. 10A)~~(Fig. 10, Upper Panel)~~. There was no response to the Aβ40-1 reverse protein. Cells from control animals did not respond to any of the Aβ proteins (Fig. 10B)~~(Fig. 10, Lower Panel)~~.

Please replace the paragraph beginning at page 62, line 12, with the following replacement paragraph:

Preparation of the pBx6 protein: An expression plasmid encoding pBx6, a fusion protein consisting of the 100-amino acid bacteriophage MS-2 polymerase N-terminal leader sequence followed by amino acids 592-695 of APP (βAPP) was constructed as described by Oltersdorf et al., J. Biol. Chem. 265, 4492-4497 (1990). The plasmid was transfected into ~~E. coli~~*E. coli* and the protein was expressed after induction of the promoter. The bacteria were lysed in 8M urea and pBx6 was partially purified by preparative SDS PAGE. Fractions containing pBx6 were identified by Western blot using a rabbit anti-pBx6 polyclonal antibody, pooled, concentrated using an Amicon Centriprep tube and dialysed against PBS. The purity of the preparation, estimated by Coomassie Blue stained SDS PAGE, was approximately 5 to 10%.

Please replace the paragraph beginning on page 68 , line 17 with the following replacement paragraph:

Groups of 7-9 month old PDAPP mice each are injected with 0.5 mg in PBS of polyclonal anti-Aβ or specific anti-Aβ monoclonals as shown below. The cell line designated RB44-10D5.19.21 producing the antibody 10D5 has the ATCC accession number PTA-5129, having been deposited on April 8, 2003. All antibody preparations are purified to have low endotoxin levels. Monoclonals can be prepared against a fragment by injecting the fragment or longer form of Aβ into a mouse, preparing hybridomas and screening the hybridomas for an antibody that specifically binds to a desired fragment of Aβ without binding to other nonoverlapping fragments of Aβ.

Please replace the paragraph beginning on page 83, line 14 with the following replacement paragraph:

Sixty male and female, heterozygous PDAPP transgenic mice, 8.5 to 10.5 months of age were obtained from Charles River Laboratory. The mice were sorted into six groups to be treated with various antibodies directed to Aβ. Animals were distributed to match the gender, age, parentage and source of the animals within the groups as closely as possible. As shown in Table 10, the antibodies included four murine Aβ-specific monoclonal antibodies, 2H3 (directed to Aβ residues 1-12), 10D5 (directed to Aβ residues 1-16) (details of the deposit of 10D5 are discussed in Example VI, *supra*), 266 (directed to Aβ residues 13-28 and binds to monomeric but not to aggregated AN1792), 21F12 (directed to Aβ residues 33-42). A fifth group was treated with an Aβ-specific polyclonal antibody fraction (raised by immunization with aggregated AN1792). The negative control group received the diluent, PBS, alone without antibody.

Please replace the paragraph beginning on page 107, line 26 with the following replacement paragraph:

The brain homogenates were diluted 1:10 with ice cold Casein Diluent (0.25% casein, PBS, 0.05% sodium azide, 20 μg/ml aprotinin, 5 mM EDTA pH 8.0, 10 μg/ml leupeptin) and then centrifuged at 16,000 x g for 20 min at 4 C. The synthetic Aβ protein standards (1-42 amino acids) and the APP standards were prepared to include 0.5 M guanidine and 0.1% bovine

serum albumin (BSA) in the final composition. The "total" Aβ sandwich ELISA utilizes monoclonal antibody (mAb) 266, specific for amino acids 13-28 of Aβ (Seubert, et al.), as the capture antibody, and biotinylated mAb 3D6, specific for amino acids 1-5 of Aβ (Johnson-Wood, et al), as the reporter antibody. The 3D6 mAb does not recognize secreted APP or full-length APP, but detects only Aβ species with an amino-terminal aspartic acid. The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130, having been deposited on April 8, 2003. This assay has a lower limit of sensitivity of ~50 ng/ml (11 nM) and shows no cross-reactivity to the endogenous murine Aβ protein at concentrations up to 1 ng/ml (Johnson-Wood et al., *supra*).

Amendments to the Drawings:

The first attached replacement drawing sheet (Figs. 1 and 2) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The second attached replacement drawing sheet (Figs. 3 and 4) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters. Figure 4 has been further amended to replace "retrospelenial" with "retrosplenial."

The third attached replacement drawing sheet (Figs. 5 and 6) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The fourth attached replacement drawing sheet (Figs. 7 and 8) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The fifth attached replacement drawing sheet (Fig. 9) has been amended to replace "retroslpenial" with "retrosplenial."

The sixth attached replacement drawing sheet (Fig. 10) has been amended identify the upper and lower panels of Figure 10 as Figure 10A and 10B, respectively. Figure 10 has also been amended to replace " retroslpenial" with "retrosplenial."

The seventh attached replacement drawing sheet (Figs 11 and 12) includes Fig. 11 which has been amended to include a legend.

The eighth attached replacement drawing sheet (Figs. 13 and 14) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The ninth attached replacement drawing sheet (Fig. 16) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side. Figure 16 has been further amended to replace "Anti AB" with "Anti-Abeta." Support for this amendment can be found on page 92, lines 25-33 of the specification.

The tenth replacement drawing sheet (Fig. 17) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side.

The eleventh attached replacement drawing sheet (Fig. 18) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side.

The twelfth attached replacement drawing sheet (Fig. 19) been amended to delete one of the occurrences of the sequence "VGSNKGAIIG."

The thirteenth attached replacement drawing sheet (Fig. 20) been amended to delete one of the occurrences of the sequence "VGSNKGAIIG."

Attachment: 13 Replacement Drawings Sheets